Vestibular Dysfunction in Active Duty Personnel Deployed to OEF/OIF

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Background

Events leading to Investigation

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UNITED PRESS INTERNATIONAL

Drug causing GIs permanent brain damage

By Mark Benjamin and Dan Olmsted
United Press International
Published 5/26/2004 4:19 PM

WASHINGTON, May 26 (UPI) -- Six U.S. soldiers have been diagnosed by the military with permanent brain damage from an anti-malaria drug used in Iraq and Afghanistan, and health officials must reassess its safety, a U.S. senator said.

Sen. Dianne Feinstein, D-Calif., in a letter to Health and Human Services Secretary Tommy Thompson, said the drug, called mefloquine, has "serious risks" that have not been adequately tracked by the Pentagon, the Peace Corps and other government agencies that distribute it.

"I ask that you work with the Food and Drug Administration to reassess the safety of mefloquine," Feinstein wrote Thompson in a letter dated May 24.

Feinstein told Thompson she is concerned that "six service members have been diagnosed with permanent brainstem and vestibular damage from being given this drug despite the fact that alternative drugs might have been chosen to prevent infection."

The FDA last year warned that the drug, also called Lariam, is linked to reports of suicide, though a connection has not been established. It also said some psychiatric and neurological side effects have been reported to last long after taking it. The Pentagon this year announced a new safety study of the drug, which has been used by some 20 million people worldwide, and the Department of Veterans Affairs said it will look at possible long-term effects on veterans.

According to people familiar with the situation, the six service members were diagnosed in

Preliminary Steps

- Initially: 12 cases of “Larium toxicity”
- Confirmed diagnosis with outside expert
- Background rate of dizziness/VOR dysfunction
- Developed case definition
  - Now only ten cases
- Multiple (ototoxic) exposures
- Apparent cluster in one small unit
  - 4 cases from 33-member Navy Tactical Dissemination Module (TDM) team

Methods

- Case-control study looking at multiple exposures
  - Surveyed two units stationed at AASAB at same time
    - Investigator-administered telephone survey, 188 questions
    - Navy TDM (n=33, 100%) → 4 cases
    - Army 286th ADB (n=18, ~10%) → 2 cases
  - Medical record review of cases (n=9, 75%)
  - Serum mefloquine levels (n=26, 55%)
- Mefloquine tablet testing (n=3, 43%)
- Review of clinic mobilization process

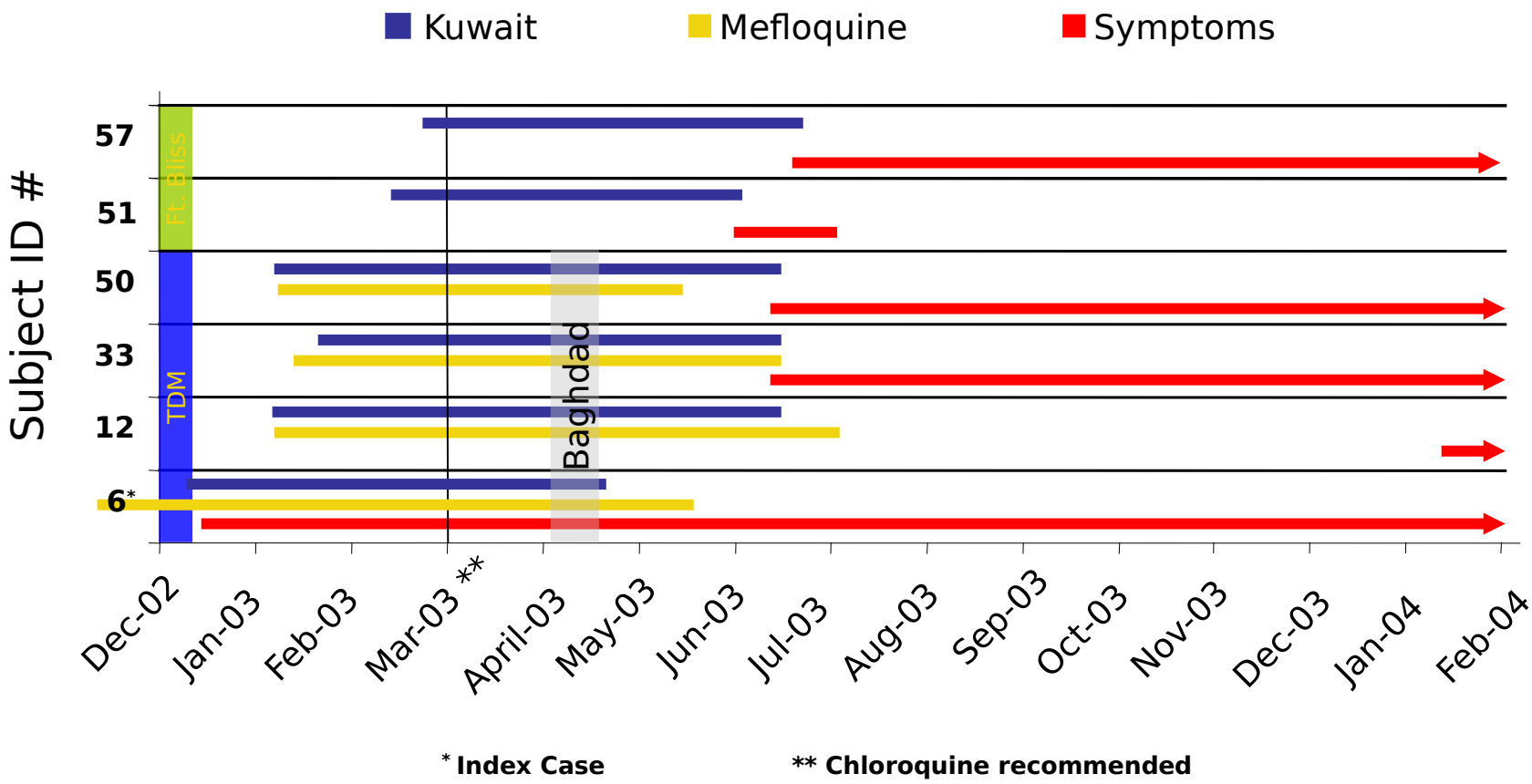
Results

Demographics & Medical History

- Overall there were no clinically significant demographic difference between cases and controls
  - ADB group was younger, active duty
- No significant difference in medical history
  - Except for PMH of motion sickness
- Cases tended to be deployed longer than controls, but not significantly

Results

Timeline of Deployment, Mefloquine Use and Symptoms for Cases



Results

Combat Stress Exposures

TDM Control Group	**Cases (n=4)** n (%)	**Controls (n=29)** n (%)	**Odds Ratio (95% CIs)**	**p-value (exact)**
Experienced extreme stress	3 (75)	10 (34)	5.7 (0.5–62.2)	0.276
Experienced intense fear	1 (25)	3 (10)	2.9 (0.2, 37.3)	0.420
See anyone killed/wounded	3 (75)	5 (17)	14.4 (1.2, 168.5)	0.036
Engaged in direct combat	1 (25)	1 (3)	9.3 (0.5, 190.6)	0.231
Great danger	4 (100)	8 (28)	---	---
ADB Control Group	**Cases (n=6)** n (%)	**Controls (n=16)** n (%)	**Odds Ratio (95% CIs)**	**p-value (exact)**
Experienced extreme stress	4 (67)	6 (37)	3.3 (0.5–24.1)	0.348
Experienced intense fear	1 (17)	3 (19)	0.9 (0.1, 10.4)	>0.99
See anyone killed/wounded	3 (50)	0	---	---
Engaged in direct combat	1 (17)	0	---	---
Great danger	5 (83)	5 (31)	11.0 (1.0, 120.4)	0.056

Results

Neuropsychiatric Symptoms (TDM group)

Variable	**Cases (n=4)** n (%)	**Controls (n=29)** n (%)	**Odds Ratio (95% CIs)**	**p-value (exact)**
Headaches	4 (100)	6 (21)	---	---
Dizziness	4 (100)	3 (10)	---	---
Unsteadiness (Walking)	3 (75)	1 (4)	66.0 (3.2, 1356.4)	0.005
Unsteadiness (Standing)	3 (75)	2 (9)	31.5 (2.1, 463.1)	0.013
Little interest in doing things	3 (75)	3 (10)	26.0 (2.0, 336.1)	0.014
Feeling down	1 (25)	3 (10)	2.9 (0.2, 37.3)	0.420
Thoughts about hurting oneself	1 (25)	n=28 1 (4)	9.0 (0.4, 184.0)	0.238
Nightmares	3 (75)	1 (3)	84.0 (4.1,1715.6)	0.003
Tried hard not to think of situations	2 (50)	1 (3)	28.0 (1.7, 458.8)	0.033
Constantly on guard	1 (25)	3 (10)	2.9 (0.2, 37.3)	0.420
Felt detached	2 (50)	2 (7)	13.5 (1.2, 153.3)	0.062

Results

Neuropsychiatric Symptoms (ADB group)

Variable	**Cases (n=6)** n (%)	**Controls (n=16)** n (%)	**Odds Ratio (95% CIs)**	**p-value (exact)**
Headaches	5 (83)	5 (31)	11.0 (1.0, 120.4)	0.056
Dizziness	6 (100)	2 (12)	---	---
Unsteadiness (Walking)	3 (50)	2 (12)	7.0 (0.8–62.0)	0.100
Unsteadiness (Standing)	3 (50)	1 (6)	15.0 (1.1–198.0)	0.046
Little interest in doing things	3 (50)	3 (19)	4.3 (0.6, 33.1)	0.283
Feeling down	2 (33)	2 (12)	3.5 (0.4, 33.3)	0.292
Thoughts about hurting oneself	1 (17)	0	---	---
Nightmares	3 (50)	2 (12)	7.0 (0.8, 62.0)	0.100
Tried hard not to think of situations	3 (50)	2 (12)	7.0 (0.8, 62.0)	0.100
Constantly on guard	2 (33)	1 (6)	7.5 (0.5, 105.3)	0.169
Felt detached	2 (33)	2 (12)	3.5 (0.4, 33.3)	0.292

Results

Malaria Chemoprophylaxis Exposures (TDM group only)

Variable	**Cases (n=4)** n (%)	**Controls (n=29)** n (%)	**Odds Ratio (95% CIs)**	**p-value (exact)**
Any antimalarial	4 (100)	23 (79)	---	---
Mefloquine Median doses (range)	4 (100) 24 (21 – 30)	15 (52) 5.7 (2 – 27)	---	---
Doxycycline	1 (25)	n=28 10 (36)	0.6 (0.1, 6.6)	>0.99
Chloroquine	0	2 (7)	---	---

Results

Chart review & Tablet Testing

- Three of 9 records reviewed had documentation of pre-deployment health assessments
- None had documentation of counseling or screening prior to issuance of mefloquine
- Post-Deployment Health Assessment in 6 of 9 charts

- Mefloquine tablets tested by FDA
  - No abnormalities in quality, constitution
  - Tablets held up well to individual issue and deployment to desert environment

Discussion

Limitations

- Small numbers (pilot study)
- Potential Bias
  - Selection bias
  - Recall bias
  - Misclassification bias

- Patient X
  - OIC of TDM group while deployed to AASAB
  - Instructed team to seek medical care if they took mefloquine
  - Informed teammates, Senator Feinstein and lay press of “link” with mefloquine
  - Currently suing Lariam manufacturer

Discussion

Biological Plausibility

- Acute neurotoxicity of mefloquine
  - Anxiety, dizziness are known acute side effects, no evidence of long-term effects
  - Disruption of endoplasmic reticulum and gap junction channels reported (Dow, 2003; Cruikshank 2004)
- Known association between anxiety disorders and vestibular dysfunction
  - Nearly 3 times as many persons with self-reported dizziness had symptoms of anxiety compared to persons without dizziness in large, U.K. study (Yardley, 1998)
  - Individuals with anxiety may exhibit abnormal findings on rotational chair testing (Rolf, 1996)
- Interaction of effects of mefloquine and combat stress?

Conclusions

- Cases had evidence of vestibular abnormalities most commonly seen with migraine or anxiety-related dizziness, and not that seen with ototoxicity.

- The rate of balance disorders and dizziness among these subjects is within the reported normal range in the general population. However, the actual rate for these disorders in an active duty population is unknown.

- No evidence that mefloquine or any known vestibulotoxic agent was associated with the vestibular dysfunction exhibited in these cases.

Conclusions

- Cases reported higher levels of combat stress and neuropsychiatric symptoms as compared to controls, suggesting that combat-related stressors may be associated with vestibular dysfunction.

- An interaction between mefloquine and combat stress cannot be ruled out

- Documentation of pre-deployment health assessments and appropriate mefloquine screening was not found in the medical records reviewed.

Recommendations

- Further study on possible interaction between mefloquine, vestibular dysfunction and combat stress
  - Exploit existing databases (pharmacy, deployment, PDHA, etc)
  - Selected survey of redeploying personnel
  - DOD-wide case finding for a larger case control study
- Establish baseline dizziness and VOR abnormality rates among active duty personnel
  - Study underway at NMCSD; 10% complete
- Re-emphasize DOD guidance regarding pre-deployment medical screening
  - Force Health Protection Prescription Products
  - Pre-Deployment Health Assessments

Acknowledgements

- **Centers for Disease Control and Prevention**
  - CAPT Peter Bloland, USPHS
  - Aaron Mendelsohn, PhD
  - CAPT Monica Parise, USPHS
  - LCDR Snehal Shah, USPHS

- **Navy Environmental and Preventive Medicine Unit FIVE**
  - CAPT Dean Bailey, MC, USN
  - LCDR Julie Howe, MC, USN
  - LCDR Andrew Vaughn, MC, USN
  - LCDR Todd Wagner, MC, USN

- **Navy Health Research Center**
- **Defense Medical Surveillance System (AMSA)**
- **Food and Drug Administration**

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BACKUP SLIDES

Background

Events prior to investigation

- Fort Bragg suicides/homicides
- Lay press reports
- AFEB recommendation
  - Keep mefloquine
- VA letter
- Blue ribbon panel

- Mefloquine recall to wholesale level secondary to possible contamination

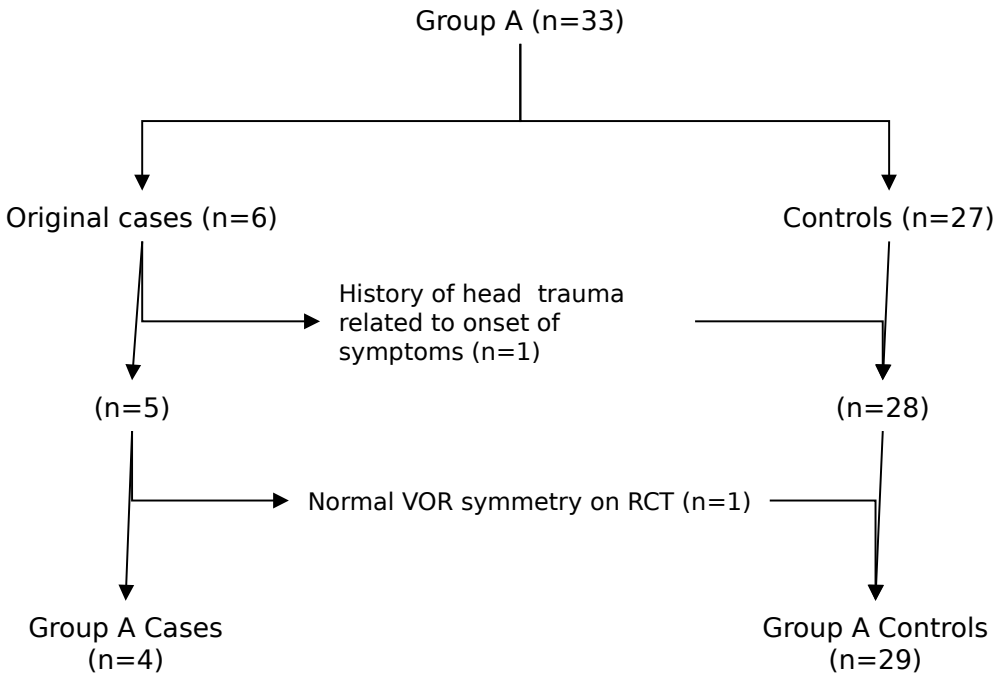
Methods

Case Definition

- Cases must be DOD Personnel (active duty, reserve, or civilian) deployed as part of Operation Iraqi Freedom or Operation Enduring Freedom since January 1, 2002, **and**
- Report new onset of dizziness during or after deployment lasting two weeks or more as a single episode or multiple episodes, **and**
- Have no other identifiable etiology including, vestibular neuronitis, Meniere's disease, head trauma, acoustic neuroma, benign paroxysmal positional vertigo (BPPV), labyrinthitis, or prior ear surgery, **and**
- Demonstrate unsteadiness of gait while walking or while standing still on physical exam, **and**
- Have VOR asymmetry on Rotational Chair Testing independently confirmed by two subject matter experts.

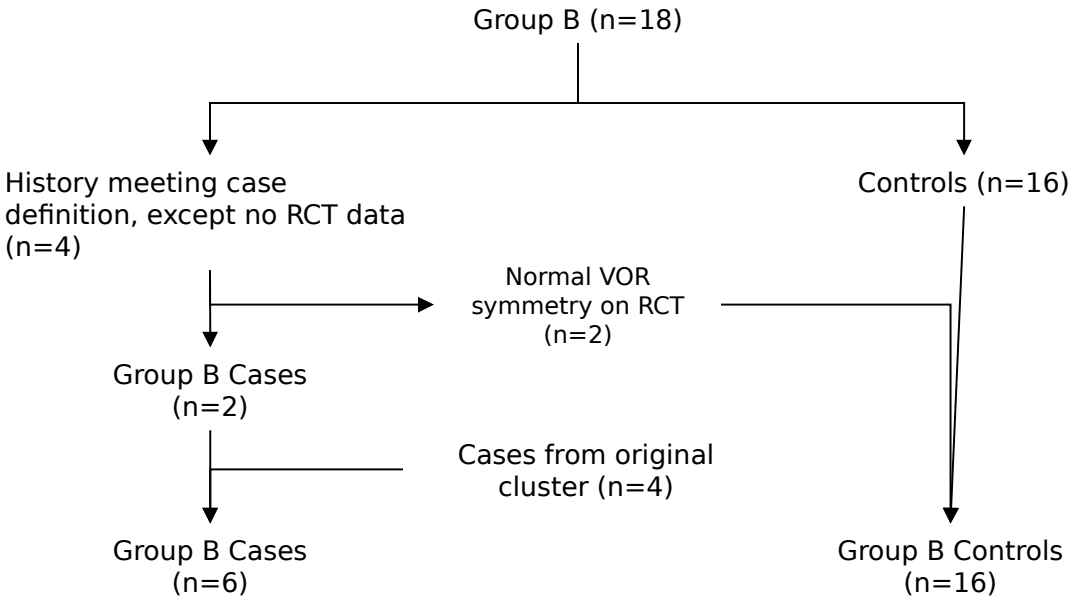
Methods

Case Selection (Tactical Dissemination Module)



Methods

Case Selection (Air Defense Battery)



Methods

Survey

- Deployment history
- Medical history
- Medication history
- Environmental exposure history
- Symptoms
- Combat stress history
- 188 questions total

Methods

Tablet Analysis

- 7 individuals reported leftover tablets available
- 3 individual actually sent tablets in for testing
- Sent to FDA for analysis